NIH clinical research studies

Protocol Number: 96-C-0147

Active Accrual, Protocols Recruiting New Patients

Title: Phase I/II Study of **tac**-Expressing Adult T-Cell Leukemia (ATL) with Yttrium-90 (90Y)-Radiolabeled Humanized **anti-tac** Monoclonal **anti**body and Calcium-DTPA

Number: 96-C-0147

Summary: This is a dose-finding study to estimate the maximum tolerated dose (MTD) of yttrium-90-labeled humanized monoclonal **anti**body **anti-tac** (90Y-MOAB **anti-tac**).

All patients receive intravenous 90Y-MOAB **anti-tac** once every 6 weeks with a fixed dose of calcium-DTPA given for 3 days; the quantity of **anti-tac** protein administered is determined by individual serum interleukin-2 receptor levels. Groups of 3-6 patients receive escalated doses of yttrium-90 until the MTD is determined. Additional patients are treated at the MTD.

Patients without evidence of disease progression or circulating **anti**bodies to humanized **anti-tac** may receive up to 8 further treatments that are at least 6 weeks apart and at least 1 week after the cessation of G-CSF therapy (if given to increase neutrophil count).

Patients are followed 4-6 weeks after the therapy is completed.

Sponsoring Institute:
National Cancer Institute (NCI)

Recruitment Detail
Type: Active Accrual Of New Subjects
Gender: Male & Female

Referral Letter Required: No

Population Exclusion(s): None

Eligibility Criteria:

DISEASE CHARACTERISTICS:

Histologically confirmed adult T-cell leukemia or lymphoma (ATL) of any stage.0

tac expression of malignant cells confirmed by one of the following: At least 10% of peripheral blood, lymph node, or dermal malignant cells reactive with **anti-tac** by immunofluorescent staining.

Soluble interleukin-2 receptor levels greater than 1,000 U/mL (normal geometric mean = 235; 95% confidence intervals = 112-502 U/mL).

Measurable disease required. More than 10% (i.e., strongly **tac**-expressing) abnormal cells in peripheral blood considered measurable disease.

No smoldering ATL, defined as:

Lymphocyte count less than 4,000;

Less than 5% abnormal lymphocytes on morphologic exam of peripheral blood;

No hypercalcemia;

Lactate dehydrogenase no greater than 1.5 times normal;

No lymphadenopathy;

No involvement of extranodal organs except skin or lung;

No malignant pleural effusion or ascites.

No symptomatic CNS disease due to ATL. Concurrent diagnosis of tropical spastic paraparesis allowed.

No detectable levels (i.e., greater than 250 ng/mL) of **anti**body to study drug as assessed by ELISA.

PRIOR/CONCURRENT THERAPY:

At least 4 weeks since cytotoxic chemotherapy.

Concurrent corticosteroids allowed.

PATIENT CHARACTERISTICS:

Age: 18 and over.

Performance status: Not specified.

Life expectancy: More than 1 month.

HEMATOPOIETIC:

AGC at least 1,000.

Platelets at least 75,000.

HEPATIC:

Bilirubin less than 2.0 mg/dL (unless directly due to ATL).

AST/ALT less than 2.5 times normal.

RENAL:

Creatinine less than 2.5 mg/dL OR;

Creatinine clearance greater than 35 mL/min.

Cardiovascular: No clinical cardiac failure.

Pulmonary: No symptomatic pulmonary dysfunction unless due to underlying malignancy.

OTHER:

No HIV **anti**body.

No pregnant or nursing women.

Negative pregnancy test required of fertile women.

Special Instructions:

Many protocols are potentially hazardous, are intended only for use by clinical oncologists in carefully structured settings, and may not prove to be more effective than standard treatment. A responsible investigator associated with this protocol should be consulted before using this protocol. Dose and schedule modifications are required for patients who develop gastrointestinal, hematologic, neurologic, and biochemical (renal, hepatic, etc.) and/or other abnormalities after the administration of therapy. Additionally, Federal regulations for the protection of human subjects require approval of clinical trials by your local Institutional Review Board.

Disease Category:

Neoplasms

Keywords:

IL-2 Receptor
G-CSF (Granulocyte Colony-Stimulating Factor)

HTLV-I
Indium-111
Calcium-DTPA

Recruitment Keywords:
None

Investigational Drug(s):
Yttrium-90 Humanized **anti-tac**
Calcium

Investigational Device(s): None

Contacts:

Patient Recruitment and Public Liaison Office, CC.
Building 61
10 Cloister Court
Bethesda, Maryland 20892-4754
Long Distance Calls: 1-800-411-1222
Fax: (301) 480-9793
Electronic Mail:prpl@mail.cc.nih.gov

Citations:

Waldmann. 1988. Therapy of patients with human T-cell lymphotrophic virus I-induced adult T-cell leukemia with **anti-tac**, a monoclonal **anti**body to the receptor for interleukin-2, *Blood, Vol. 72*, p. 1805

Kozak. 1989. The nature of the bifunctional chelating agent used for radioimmunotherapy with Yttrium-90 monoclonal **anti**bodies is a critical factor in determining in vivo survival and organ toxicity, *Cancer Res, Vol. 49*, p. 2639

Waldmann. 1995. Radioimmunotherapy of interleukin-2Rx-expressing adult T-cell leukemia with yttrium-90-labeled **anti-tac**, *Blood, Vol. 86*, p. 4063

Active Accrual, Protocols Recruiting New Patients

If you have:

- Questions about participating in a study, please contact the Patient Recruitment and Public Liaison Office, CC.
- Questions about specific studies, or the database in general, please contact the Protocol Coordination Service Center, CC.
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Blood 72: 1805-1816 (1988)[PMID2846094,MUID89027118]

Therapy of patients with human T-cell lymphotrophic virus I-induced adult T-cell leukemia with anti-Tac, a monoclonal antibody to the receptor for interleukin-2.

T. A. Waldmann, C. K. Goldman, K. F. Bongiovanni, S. O. Sharrow, M. P. Davey, K. B. Cease, S. J. Greenberg & D. L. Longo

Metabolism Branch, National Cancer Institute, Bethesda, MD 20892.

Human T-cell lymphotropic virus I (HTLV-I)-induced adult T-cell leukemia (ATL) cells constitutively express interleukin-2 (IL-2) receptors identified by the anti-Tac monoclonal antibody (MoAb), whereas normal resting cells do not. This observation provided the scientific basis for a trial of intravenous anti-Tac in the treatment of nine patients with ATL. The patients did not suffer untoward reactions and did not have a reduction in the normal formed elements of the blood, and only one of the nine produced antibodies to the anti-Tac MoAb. Three patients had transient mixed, partial, or complete remissions lasting from 1 to more than 8 months after anti-Tac therapy, as assessed by routine hematologic tests, immunofluorescence analysis of circulating cells, and molecular genetic analysis of HTLV-I provirus integration and of the T-cell receptor gene rearrangement. The precise mechanism of the antitumor effects is unclear; however, the use of a MoAb that prevents the interaction of IL-2 with its receptor on ATL cells provides a rational approach for the treatment of this malignancy.

Cancer Res **49:** 2639-2644 (1989)[PMID2785435,MUID89230284]

Nature of the bifunctional chelating agent used for radioimmunotherapy with yttrium-90 monoclonal antibodies: critical factors in determining in vivo survival and organ toxicity.

R. W. Kozak, A. Raubitschek, S. Mirzadeh, M. W. Brechbiel, R. Junghaus, O. A. Gansow & T. A. Waldmann

Division of Cytokine Biology, Center for Biologics Evaluation and Research, FDA, Bethesda, Maryland.

One factor that is critical to the potential effectiveness of radioimmunotherapy is the design of radiometal-chelated antibodies that will be stable in vivo. Stability in vivo depends on the condition that both the chelate linkage and radiolabeling procedures not alter antibody specificity and biodistribution. In addition, synthesis and selection of the chelating agent is critical for each radiometal in order to prevent inappropriate release of the radiometal in vivo. In the present study, we compare the in vivo stability of seven radioimmunoconjugates that use different polyaminocarboxylate chelating agents to complex yttrium-88 to the mouse anti-human interleukin-2 receptor monoclonal antibody, anti-Tac. Chelate linkage and radiolabeling procedures did not alter the immunospecificity of anti-Tac. In order to assess whether yttrium was inappropriately released from the chelate-coupled antibody in vivo, iodine-131-labeled and yttrium-88 chelate-coupled antibodies were simultaneously administered to the same animals to correlate the decline in yttrium and radioiodinated antibody activity. The four stable yttrium-88 chelate-coupled antibodies studied displayed similar iodine-131 and yttrium-88 activity, indicating minimal elution of yttrium-88 from the complex. In contrast, the unstable yttrium-88 chelate-coupled antibodies had serum yttrium-88 activities that declined much more rapidly than their iodine-131 activities, suggesting loss of the radiolabel yttrium-88 from the chelate. Furthermore, high rates of yttrium-88 elution correlated with deposition in bone. Four chelating agents emerged as promising immunotherapeutic reagents: isothiocyanate benzyl DTPA and its derivatives 1B3M, MX, and 1M3B. All four isothiocyanate agents showed prolonged yttrium-88 vascular survival which was essentially identical to that of their iodine-131 activity with only minimum accumulation (1.4-1.8%/g) of the yttrium-88 injected dose into bone. Thus, these four chelating agents were very stable in vivo and suitable for yttrium-monoclonal antibody radioimmunotherapy.

Blood **86:** 4063-4075 (1995)[PMID7492762,MUID96082159]

Radioimmunotherapy of interleukin-2R alpha-expressing adult T-cell leukemia with Yttrium-90-labeled anti-Tac.

T. A. Waldmann, J. D. White, J. A. Carrasquillo, J. C. Reynolds, C. H. Paik, O. A. Gansow, M. W. Brechbiel, E. S. Jaffe, T. A. Fleisher, C. K. Goldman & ...

Metabolism Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.

Adult T-cell leukemia (ATL) is a malignancy of mature lymphocytes caused by the retrovirus human T-cell lymphotropic virus-I. It is an aggressive leukemia with a median survival time of 9 months; no chemotherapy regimen appears successful in inducing long-term disease-free survival. The scientific basis of the present study is that ATL cells express high-affinity interleukin-2 receptors identified by the anti-Tac monoclonal antibody, whereas normal resting cells do not. To exploit this difference, we administered anti-Tac armed with Yttrium-90 (90Y) to 18 patients with ATL initially (first 9 patients) in a phase I dose-escalation trial and subsequently (second group of 9 patients) in a phase II trial involving a uniform 10-mCi dose of 90Y-labeled anti-Tac. Patients undergoing a remission were permitted to receive up to eight additional doses. At the 5- to 15-mCi doses used, 9 of 16 evaluable patients responded to 90Y anti-Tac with a partial (7 patients) or complete (2 patients) remission. The responses observed represent improved efficacy in terms of length of remission when compared with previous results with unmodified anti-Tac. Clinically meaningful (> or = grade 3) toxicity was largely limited to the hematopoietic system. In conclusion, radioimmunotherapy with 90Y anti-Tac directed toward the IL-2R expressed on ATL cells may provide a useful approach for treatment of this aggressive malignancy.

NIH clinical research studies

Protocol Number: 83-C-0023

Active Accrual, Protocols Recruiting New Patients

Title: Preliminary Feasibility Study of Monoclonal **anti-tac anti**body Immunotherapy of Adult T-Cell Leukemia (ATL)

Number: 83-C-0023

Summary: Nonrandomized study.

Immunotherapy. Monoclonal **anti-tac anti**body, **anti-tac**.

Sponsoring Institute:
National Cancer Institute (NCI)

Recruitment Detail
Type: Active Accrual Of New Subjects
Gender: Male & Female

Referral Letter Required: No

Population Exclusion(s): None

Eligibility Criteria:
Disease Characteristics:

Histologically confirmed leukemia or lymphoma (including cutaneous T-cell lymphoma and adult T-cell leukemia)

Reactivity of at least 10% of peripheral blood T cells or lymph node cells with **anti-tac** as determined by immunofluorescent staining required Meningeal lymphomatous involvement as determined by the presence of malignant cells in the CSF allowed (such patients receive therapy such as intrathecal methotrexate and CNS irradiation as appropriate).

Prior/Concurrent Therapy:

Biologic Therapy: Not specified.

Chemotherapy: Prior chemotherapy allowed More than 3 weeks since prior chemotherapy.

Endocrine Therapy: Not specified.

Radiotherapy: More than 3 weeks since prior radiotherapy.

Surgery: Not specified.

Patient Characteristics:

Age: 18 and over.

Performance status: Not specified.

Life expectancy: At least 2 months.

Hematopoietic: Not specified.

Hepatic: Not specified.

Renal: Not specified.

Special Instructions:

Many protocols are potentially hazardous, are intended only for use by clinical oncologists in carefully structured settings, and may not prove to be more effective than standard treatment. A responsible investigator associated with this protocol should be consulted before using this protocol. Dose and schedule modifications are required for patients who develop gastrointestinal, hematological, neurologic, and biochemical (renal, hepatic, etc.) and/or other abnormalities after the administration of therapy. Additionally, Federal regulations for the protection of human subjects require approval of clinical trials by your local Institutional Review Board.

Disease Category:

Neoplasms

Keywords:

Adult T-Cell Leukemia (ATL)
anti-tac antibody

Recruitment Keywords:

None

Investigational Drug(s):

Monoclonal **anti**body **(anti-tac)**

Investigational Device(s): None

Contacts:

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10 Cloister Court
Bethesda, Maryland 20892-4754
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Fax: (301) 480-9793
Electronic Mail:prpl@mail.cc.nih.gov

Citations:

Uchiyama. 1981. A monoclonal **anti**body **(anti-tac)** reactive with activated and functionally mature T cells, *J Immunol, Vol. 126*, p. 1398

Leonard. 1982. A monoclonal **anti**body that appears to recognize the receptor for human T-cell growth factor; partial characterization of the receptor, *Nature, Vol. 300*, p. 267

Uchiyama. 1977. Adult T-cell leukemia: Clinical and hematological features of 16 cases, *Blood, Vol. 50*, p. 481

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J Immunol **126**: 1398-1403 (1981)[PMID6451645,MUID81143482]

A monoclonal antibody (anti-Tac) reactive with activated and functionally mature human T cells. II. Expression of Tac antigen on activated cytotoxic killer T cells, suppressor cells, and on one of two types of helper T cells.

T. Uchiyama, D. L. Nelson, T. A. Fleisher & T. A. Waldmann
